Screening for Renal Artery Stenosis

"Open renal arteries are better than closed renal arteries."

White, Cath Cardiovasc Diagn, 1998

(If you can find the closed ones…)

The Language of Screening

TP + FP
= All Pos

FN + TN
= All Neg

TP + FN =
Total w/ disease

FP + TN =
Total w/o disease

The Language of Screening

Prevalence = (TP + FN)/(TP + FN + FP + TN)

Sensitivity = TP/(TP + FN)

Specificity = TN/(TN + FP)

False Neg Rate = FN/(TP + FN), or

1-sensitivity

False Pos Rate = FP/(TN +FP), or

1- specificity

Harrison's Principals of Internal Medi
ed. Braunwald, p8, 1987

The Language of Screening

Positive Predictive Value = TP/(TP + FP)

Negative Predictive Value = TN/(TN + FN)

Accuracy = (TP + TN)/(TP + FP + TN + FN)

Harrison's Principals of Internal Medicine, 11th ed. Braunwald, 1987

The Language of Screening

Sensitivity and specificity do not depend on prevalence. They are characteristic of the test, which in turn employs certain disease features. Tests must be validated in different populations, especially if disease features vary.

In RAS screening, sensitivity and specificity for some tests can be affected by:

- Renal Insufficiency
- Bilateral vs. unilateral stenosis
- Presence or absence of hypertension

The Language of Screening

Predictive value depends on prevalence.

- A given test administered to a high prevalence population has a higher positive predictive value and lower negative predictive value, than when administered to a low prevalence population.
- Most tests for RAS are studied in “enriched”, high prevalence populations.

You must do a “gold standard test” to determine all these “values”! Really!

Renal Artery Stenosis What are we screening for?

- Renal Artery Stenosis
  - A radiologic diagnosis which may or may not be functionally important
    - Atherosclerotic and progressive
    - FMD, less likely to progress
  - Functional significance--? stenosis > 50-75%, post-stenotic dilatation, collateral vessels
  - Anatomic studies are best--i.e., arteriogram, duplex US, MRA

Wilcox, Sem Neph 16: 43, 1996

Renal Artery Stenosis What are we screening for?

- Renovascular Hypertension
  - A functional diagnosis: HTN improved or cured by reversal of RAS. Can be unsatisfactory because:
    - HTN may become incurable (JASN, 4:529, 1993)
    - Lack of successful intervention.
  - Therefore functional studies (renin; captopril test, captopril scintigraphy) may not correlate with anatomic studies.

Wilcox, Sem Neph 16: 43, 1996

Renal Artery Stenosis What are we screening for?

- Ischemic Nephropathy
  - Loss of renal function or parenchyma caused by hemodynamic changes resulting from RAS.
  - Diagnosis almost always made in context of coexisting hypertension; would otherwise often go unsuspected.
  - No good screening tests; existing tests designed for screening for renovascular HTN

Wilcox, Sem Neph 16: 43, 1996

RAS
What are we screening for?

- When reading the literature it is, therefore, important to determine what the authors were actually screening for:
  - Anatomic stenosis? Arteriography is the gold standard.
  - Functional stenosis? Reversible HTN or azotemia upon revascularization is the gold standard.

Renal Artery Stenosis Who should we screen?

- Patients suspected of having renovascular hypertension
  - Available studies are designed for this
  - Prevalence is ≤ 0.5% among general hypertensive population. (Mann and Pickering, Ann Int Med. 117:845, 1992)
  - Screening should be directed toward those with a history suggestive of the diagnosis

Renal Artery Stenosis Who should we screen?

- Patients suspected of having ischemic nephropathy
  - Available studies are not designed for this--and we don't know how to screen for it!
  - Prevalence is unknown. (Mann and Pickering, Ann Int Med. 117:845, 1992)
  - This disease may present with a history c/w with renovascular HTN, with azotemia, or be largely insidious and unexpected.

Renal Artery Stenosis Who should we screen?

- Patients with a suggestive HTN history!
  - Features not typical of essential HTN or renal failure not typical of nephrosclerosis (Mann & Pickering, 1992).
- Cooperative Study of RVH (JAMA, 1972)
  - 2442 HTN patients assessed with clinical characteristics, physical, lab and diagnostic tests
  - 339 with “essential HTN”: nl a-gram; nl renal fxn
  - 175 with “RVH” : defined by surgical cure

Renal Artery Stenosis Who should we screen?

- Significant Differences between Patients with RVH and Those with Essential HTN:
  - Older age of onset: 35 ± 11 vs. 46 ± 12 yrs
  - Shorter duration: 3.1 vs. 1.9 yrs.
  - Accelerated HTN: 13% vs. 23%
  - CAD/CVD/PVD: 10% vs. 20%
  - High grade retinopathy/malignant HTN: 12% vs. 26%
  - Abdominal bruit: 7% vs. 41%

JAMA. 220:1195, 1209 (1972)

Renal Artery Stenosis Who should we screen?

- Duke University Study (JASN. 2:1608, 1992)
  - Prospective study of 1235 patients undergoing cardiac cath. 15% had RAS > 50%.
  - Factors predictive of RAS by multivariate analysis:
    - Older age
    - Greater degree of coronary disease
    - CHF
    - Peripheral vascular disease
    - Male gender was a NEGATIVE predictor!

Renal Artery Stenosis Who should we screen?

- Patients with ACE inhibitor-induced acute renal failure (Van de Ven, KI 53:986, 1998)
  - Prospective study of 108 patients with high risk for RAS. 50% had bilateral RAS by a-gram. 20% increase in creatinine with ACEI was 100% sensitive for bilateral RAS, with 70% specificity.
- Poorly controlled BP (J. HTN, 14:1033, 1996)
  - BP_S > 160; BP_D > 100 mm Hg determined an subgroup of patients with RAS prevalence of 30%.

Renal Artery Stenosis Who should we screen?

- Patients with BP not responsive to 2 drugs or with 10% rise in serum creatinine with ACE inhibitors have an ↑prevalence of RAS (22%) by a-gram. (DRASTIC Trial. Contrib Nephrol 119:54, 1996)
- DRASTIC clinical prediction rule development (Ann Int Med. 129:705, 1998)
  - 1133 patients screened by above “rule”--439 “failed”.
  - Angiography and renal scintigraphy in “failures”.
  - Multicenter study in Holland, very few black patients.

Renal Artery Stenosis Who should we screen?

Multivariate Analysis of risk factors chosen from literature. Those that were “predictive” of RAS:

- Increasing age
- Female sex (!)
- CAD/CVD/PVD
- Recent onset HTN
- History of smoking
- Abdominal bruit (very strong predictor)
- Increased serum creatinine
- Hypercholesterolemia
- Absence of Obesity (!)

Ann Int Med.129:705, 199

Renal Artery Stenosis How should we screen?

- So you have determined your patient is at risk…
- **Stratify before you screen!**
  - Mann and Pickering (Ann Int Med;117:845, 1992) recommend stratifying into 3 groups based on index of clinical suspicion (read "prevalence"), so as to maximize the predictive value of the available tests

Mann and Pickering Stratification System

Clinical Suspicion	Prevalence	+ Pred Value of Captopril Scan (≈ Sens = 93% and Spec = 95%)
LOW Absent Clinical Clues	0.2-1%	4-16% (very poor, don't screen)
MODERATE Severe/abrupt onset HTN, PVD/CAD, atypical age onset, stable azotemia	5-15%	50-77%, with high neg pred value (99%)
HIGH Severe, refractory HTN with progressive azotemia, typical bruit, renal asymmetry, ACEI-induced ARF	25-50%	86-95%, may proceed direct to a-gram

How to Screen
Available Screening Tests for RAS

- Tests based on physiologic/functional abnormality
  - Rapid Sequence IVP
  - PRA
  - Captopril Test
  - Renal Vein Renins
  - Captopril Scintigraphy
- Tests based on anatomy
  - Duplex US
  - MRA
  - Arteriogram
- Tests based on clinical criteria
  - Clinical Prediction rules

Warning! Warning!

The tests we are about to discuss are designed for the detection of renovascular hypertension or renal artery stenosis--NOT ischemic nephropathy

Screening: Rapid Sequence IVP

Sensitivity	≈75%
Specificity	75-85%
Advantages	Simple
Disadvantages	Large dye load; No longer recommended

Refs: Havey, JAMA. 254: 388, 1985
Thornbury, Urol Radiol. 3: 209, 1981

Screening: Plasma Renin Activity (PRA)

Sensitivity	75% to "low"
Specificity	85% to "low"
Advantages	Simple Low PRA said to be useful
Disadvantages	Not a useful test in patients with azotemia; wide variation in PRA. In Rossi study, 37% of patients with RVH had low PRA

Refs: Pickering, et al, Am J Med.76:398, 1984
Rossi, et al, Clin Sci. 93:435, 1997

Screening: Renal Vein Renin Sampling

Sensitivity	Approx. 75% -80%
Specificity	62-100%, depending on V/A ratios
Advantages	Functional test
Disadvantages	Worse sensitivity with azotemia. Requires femoral v. catheterization and fluro time. Not highly recommended.

Refs: Vaughan, et al, Am J Med. 55:402, 1973
Marks, et al, Urol Clin NA. 2:311, 1975

Screening: Captopril Test

Sensitivity 38-100%
About 50% in Cornell Scintigraphy study

Specificity 72-100%

Advantages Simple functional test that with Duplex US may help discriminate RVH vs. RAS
Miralles, et al, Am J HTN 10:1290, 1997

Disadvantages Not sensitive or specific with azotemia (s.creat > 1.5 mg%)
False positives can be seen with high renin hypertension.

Refs: Muller, et al, Am J Med. 80:633, 1986

Screening: Captopril Scintigraphy

Sensitivity	≈93% in early studies 82% in Cornell study 72% in DRASTIC study
Specificity	95% in early studies 86% Cornell study; 90% in DRASTIC
Advantages	Functional study, non-invasive study with relatively high specificity and sensitivity.
Disadvantages	Methods not uniform—i.e., tracer, qualitative vs. quantitative. May not correlate with a-gram because it is a functional test. Azotemia is a problem, as is bilateral disease.

Captopril Scintigraphy
Some Noteworthy Studies

DRASTIC trial (Ann Int Med, 129:705, 1998)

- Angiography in 439 pts. Gold STD test for RAS.
- Captopril scintigraphy also performed. Sensitivity 72%, Specificity 90%.

Einstein-Cornell Study (J Nuc Med, 39:522, 1998)

- 60 pts with high probability of RVD vs. 43 with "essential HTN". Captopril scintigraphy performed in all (DTPA and OIH), angiogram with PTCA in all 60 subjects. Gold STD test was cure of BP after PTCA.
- Qualitative scintigraphy with 82% sensitivity, 86% specificity, but hindered by about 50% non-diagnostic studies.
- Accuracy was about 58% for both OIH and DTPA

Captopril Scintigraphy
Some Noteworthy Studies

Van Jaarsveld (Arch Int Med, 157:1226, 1997)

- Angiography in 505 pts. Prevalence 52%. Gold STD test for RAS.
- Scintigraphy with and without captopril performed. Sensitivity about 67% regardless of captopril, Specificity 90%.
- Mag3 not significantly different from DTPA.

Fommei, et al (Eur J Nuc Med. 20:617, 1993)

- 280 patients, 125 with RAS by a-gram >70%, 54 BP responders to surgery or PTCA (Gold STD). Captopril scintigraphy performed in all.
- Post captopril scintigraphyalone with 95%, 100% specificity for predicting BP response, but only 83% sensitivity and 93% specificity in predicting RAS.

Screening: Duplex Ultrasound

Sensitivity	98% in Olins study, but Blaufox meta-analysis suggests similar to captopril scintigraphy
Specificity	98% in Olins study, but Blaufox suggest similar to captopril scan
Advantages	Non-invasive, theoretically more likely to correlate a-gram, than functional tests.
Disadvantages	Very operator dependent. A good study may take up to 1 hour.

Refs: Olins, et al, Ann Int Med. 122:833, 1995
Blaufox, et al, J Nuc Med. 37: 171, 1996

Screening: MRA

Sensitivity	93-100% sensitivity for proximal renal arteries
Specificity	90-96% for proximal renal arteries
Advantages	Non-invasive, anatomic study.
Disadvantages	Still in development. Tends to undercall accessory and mid-segment arteries May overcall main renal artery stenoses.

Refs: Olins, et al, Ann Int Med. 122:833, 1995
Blaufox, et al, J Nuc Med. 37: 171, 1996

Screening: Clinical Prediction Rules

- DRASTIC study (Ann Int Med, 129:705, 1998)
  - Using the results of the multivariate analysis already discussed, this group developed a clinical prediction rule (scoring system) to predict RAS as defined by a-gram. Internally, but not yet externally validated. High ROC value.
  - Choosing a score threshold that predicts a 30% probability of stenosis yielded a test with sensitivity of 68% and a specificity of 87%--about as good a Captopril scintigraphy in the same group of patients.
  - Requires outside validation, but attractive concept!

What to Do?

- Mann and Pickering Algorithm (simplified by me, and assuming a reasonable life expectancy!)
  - Low clinical probability→ No work-up
  - High clinical probability→ Consider arteriogram directly
  - Moderate probability→ Captopril renogram or duplex US
    - If positive, go to arteriogram.
    - If negative, no further work-up.

The cost of doing business...

Blaufox, et al, J Nuc Med, 37:171, 1996

- Meta-analysis assessing cost effectiveness of various approaches to RVH diagnosis and treatment
- Assessed arteriography, scintigraphy, Doppler, and captopril test
- Cost per patient cured/improved vs. lifetime medical tx
- Assumed an RAS prevalence of 30%, 77% cure rate
- Number diagnoses/cost per cure was calculated; this represents the relative value of the test.
- Captopril renography and a-gram were similar, and life-time savings of $5000-8000 dollars could be accrued with angioplasty, but not surgery.